L5 ANSWER 1 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:795665 CAPLUS
DOCUMENT NUMBER: 132:30824
TITLE: Pharmaceutical composition with **tumor** necrosis factor-.alpha. or other biological response modifier and 2-methoxyestrone-3-O-sulphamate for inhibition of estrone sulphatase and treatment of **cancer**
INVENTOR(S): Reed, Michael John; Potter, Barry Victor Lloyd
PATENT ASSIGNEE(S): Sterix Limited, UK
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964013	A1	19991216	WO 1999-GB1835	19990610 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2334119	AA	19991216	CA 1999-2334119	19990610 <--
AU 9942807	A1	19991230	AU 1999-42807	19990610 <--
EP 1085876	A1	20010328	EP 1999-955428	19990610
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002517449	T2	20020618	JP 2000-553081	19990610

PRIORITY APPLN. INFO.: GB 1998-12535 A 19980610
GB 1999-10167 A 19990430
WO 1999-GB1835 W 19990610
OTHER SOURCE(S): MARPAT 132:30824
AB The compn. comprises a sulfamate compd., e.g. 2-methoxyestrone-3-O-sulfamate, and a biol. response modifier, e.g., TNF. The compn. is useful for the prevention and/or treatment of **cancer**.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:736476 CAPLUS
DOCUMENT NUMBER: 131:346535
TITLE: Use of neomycin for treating angiogenesis-related diseases
INVENTOR(S): Hu, Guo-Fu; Vallee, Bert L.
PATENT ASSIGNEE(S): The Endowment for Research In Human Biology, Inc., USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958126	A1	19991118	WO 1999-US10269	19990511 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2331620	AA	19991118	CA 1999-2331620	19990511	<--
AU 9939804	A1	19991129	AU 1999-39804	19990511	<--
EP 1083896	A1	20010321	EP 1999-922915	19990511	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
US 6482802	B1	20021119	US 2000-700436	20001109	
PRIORITY APPLN. INFO.:			US 1998-84921P	P 19980511	
			WO 1999-US10269	W 19990511	

AB The present invention is directed to using neomycin or an analog thereof as a therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compns. comprising: (a) neomycin or an analog and, optionally, (b) another anti-angiogenic agent or an anti-**neoplastic** agent. The present invention is further directed to a method for screening neomycin analogs having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases. A dose of 20 ng neomycin/embryo or higher completely inhibited angiogenin-induced angiogenesis in the chorioallantoic membrane (CAM) assay. Neomycin inhibits angiogenin-induced angiogenesis mainly through inhibition of nuclear translocation of angiogenin.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:8267 CAPLUS
DOCUMENT NUMBER: 132:146811
TITLE: DNA damage induced by catecholestrogens in the presence of copper (II): generation of reactive oxygen species and enhancement by NADH
AUTHOR(S): Thibodeau, P. A.; Paquette, B.
CORPORATE SOURCE: Faculty of Medicine, Department of Radiobiology, Universite de Sherbrooke, Sherbrooke, QC, Can.
SOURCE: Free Radical Biology & Medicine (**1999**), 27(11/12), 1367-1377
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Certain estrogen metabolites are involved in carcinogenesis and the development of resistance to methotrexate (MTX). In this study, the authors detd. whether these well-established biol. effects correlate with the relative efficiency of several estrogen metabolites to induce DNA strand breaks in the presence of copper, and investigated the potential enhancing effect of reduced NAD (NADH). DNA strand breaks induced by estradiol metabolites were measured by the conversion of supercoiled phage .phi.X-174 RF1 DNA to open circular and linear forms. The most active catecholestrogens were the 4-hydroxy derivs., which produced about 2.5 times more DNA double strand breaks than the 2-hydroxy derivs., while estradiol and 16.alpha.-hydroxyestrone were inactive. In addn., the authors' results show that 4-hydroxyestradiol (4-OHE2) at physiol. concns. was capable of exhibiting DNA cleaving activity. The formation of these catecholestrogen-induced DNA strand breaks was assocd. with the utilization of oxygen and the generation of H2O2, because catalase

inhibited the DNA cleaving activity of 4-OHE2. Interestingly, the authors also obsd. that NADH enhanced the induction of DNA strands breaks by 4-OHE2/Cu(II), probably by perpetuating the redox cycle between the quinone and the semiquinone forms of the catecholestrogen. In conclusion, this study demonstrated that the relative efficiency of 2-, and 4-hydroxyestrogen in carcinogenesis and for the enhancement of MTX resistance correlates with their relative capability to induce DNA strand breaks. To inhibit these estrogen-mediated biol. effects, it may be important to develop different strategies to block the prodn. of reactive oxygen species by the catecholestrogen-redox cycle.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:438407 CAPLUS
DOCUMENT NUMBER: 131:237597
TITLE: Inhibition of **tumor** necrosis factor .alpha.-stimulated aromatase activity by microtubule-stabilizing agents, paclitaxel and 2-methoxyestradiol
AUTHOR(S): Purohit, A.; Singh, A.; Ghilchik, M. W.; Reed, M. J.
CORPORATE SOURCE: Endocrinology and Metabolic Medicine, Imperial College School of Medicine, St Mary's Hospital, London, W2 1NY, UK
SOURCE: Biochemical and Biophysical Research Communications (**1999**), 261(1), 214-217
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aromatase enzyme, which converts androstenedione to estrone, regulates the availability of estrogen to support the growth of hormone-dependent breast **tumors**. Cytokines, such as interleukin 6 (IL-6) and **tumor** necrosis factor .alpha. (TNF.alpha.) or prostaglandin E2 (PGE2), can stimulate aromatase activity. These factors may originate from cells of the immune system that infiltrate breast **tumors**. Paclitaxel, which is used in the treatment of breast **cancer**, stabilizes microtubules and has previously been shown to rapidly down-regulate TNF-receptors on human macrophages. The endogenous estrogen metabolite, 2-methoxyestradiol (2-meOE2), also acts to stabilize microtubules. In this study, we have examd. the ability of paclitaxel or 2-meOE2 to antagonize TNF.alpha.-stimulated aromatase activity in stromal fibroblasts derived from normal or malignant breast tissues. Paclitaxel inhibited basal and TNF.alpha.-stimulated aromatase activities by 88% and 91% resp. 2-MeOE2 also reduced basal and TNF.alpha.-stimulated aromatase activities by 46% and 56% resp. Both paclitaxel and 2-meOE2 also inhibited stimulation of aromatase activity by IL-6 plus its sol. receptor and PGE2. The 16.alpha.-hydroxylated deriv. of 2-meoE2 and 2-meOE3, which does not bind to microtubules, was less effective at inhibiting TNF.alpha.-stimulated aromatase activity. Increased 2-hydroxylation of estrogens, and subsequent formation of their 2-methoxy derivs., may be assocd. with a reduced risk of breast **cancer**. It is possible that the pathway of estrogen metab. may influence the ability of stromal cells to respond to cytokine stimulation. (c) 1999 Academic Press.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:728094 CAPLUS
DOCUMENT NUMBER: 130:90647
TITLE: An agent that increases **tumor** suppressor transgene product coupled with systemic transgene delivery inhibits growth of **metastatic** lung **cancer** in vivo

AUTHOR(S): Kataoka, Masafumi; Schumacher, Guido; Cristiano, Richard J.; Atkinson, E. Neely; Roth, Jack A.; Mukhopadhyay, Tapas

CORPORATE SOURCE: Section of Thoracic Molecular Oncology, Department of Thoracic and Cardiovascular Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Cancer Research (**1998**), 58(21), 4761-4765
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: AACR Subscription Office

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Low levels of gene expression following systemic delivery have impaired the effectiveness of **tumor** suppressor gene replacement in treating **metastases**. We asked whether combined treatment with 2-methoxyestradiol (2-Me), which increases levels of wild-type p53 protein in **cancer** cells, and the systemic administration of an adenoviral vector expressing wild-type p53 (Ad-p53) would inhibit the growth of human **metastatic** lung **cancer** cells in vivo. The simultaneous administration of p53 and 2-Me resulted in a greater than additive redn. with the lung colony count reduced to 33% of its control value. These results suggest that the synergistic effect of 2-Me and Ad-p53 in combination treatment may have application in the systemic treatment of **cancer**.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:369884 CAPLUS

DOCUMENT NUMBER: 129:90490

TITLE: Is 2-methoxyestradiol an endogenous estrogen metabolite that inhibits mammary carcinogenesis?

AUTHOR(S): Zhu, Bao Ting; Conney, Allan H.

CORPORATE SOURCE: Laboratory for Cancer Research, Department of Chemical Biology, College of Pharmacy, Rutgers-The State University of New Jersey, Piscataway, NJ, 08854-8020, USA

SOURCE: Cancer Research (**1998**), 58(11), 2269-2277
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with 172 refs. Catechol estrogens (2- or 4-hydroxyestradiol and 2- or 4-hydroxyestrone) are chem. reactive estrogen metabolites that are O-methylated to less polar monomethyl ethers by catechol-O-methyltransferase, an enzyme present in many tissues such as the liver, kidney, brain, placenta, uterus, and mammary gland. In the present report, the authors review recent studies on the antitumorigenic and antiangiogenic effects of exogenously administered 2-methoxyestradiol in vitro and in vivo. The authors also discuss data that suggest that endogenous formation of 2-methoxyestradiol (and its 2-hydroxyestradiol precursor) may have a protective effect on estrogen-induced **cancers** in target organs. Although the mol. mechanism of action of 2-methoxyestradiol is not clear, the authors suggest that some unique effects of 2-methoxyestradiol may be mediated by a specific intracellular effector or receptor that is refractory to the parent hormone, estradiol. Addnl. research is needed to identify factors that regulate the metabolic formation and disposition of 2-methoxyestradiol in liver and in target cells and to evaluate the effects of modulating 2-methoxyestradiol formation on estrogen-induced carcinogenesis.

REFERENCE COUNT: 172 THERE ARE 172 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:507828 CAPLUS
DOCUMENT NUMBER: 129:212069
TITLE: Effect of steroid hormones and retinoids on the formation of capillary-like tubular structures of human microvascular endothelial cells in fibrin matrixes is related to urokinase expression
AUTHOR(S): Lansink, Mirian; Koolwijk, Pieter; Van Hinsbergh, Victor; Kooistra, Teake
CORPORATE SOURCE: Gaubius Laboratory TNO-PG, Leiden, 2301 CE, Neth.
SOURCE: Blood (**1998**), 92(3), 927-938
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiogenesis, the formation of new capillary blood vessels, is a feature of a variety of pathol. processes. To study the effects of a specific group of hormones (all ligands of the steroid/retinoid/thyroid hormone receptor superfamily) on the angiogenic process in humans, the authors have used a model system in which human microvascular endothelial cells from foreskin (hMVEC) are cultured on top of a human fibrin matrix in the presence of basic fibroblast growth factor and **tumor** necrosis factor-.alpha.. This model mimics the in vivo situation where fibrin appears to be a common component of the matrix present at sites of chronic inflammation and **tumor** stroma. The authors' results show that testosterone and dexamethasone are strong inhibitors and all-trans retinoic acid (at-RA) and 9-cis retinoic acid (9-cis RA) are potent stimulators of the formation of capillary-like tubular structures. These effects are mediated by their resp. nuclear hormone receptors as demonstrated by the use of specific synthetic receptor agonists and antagonists. 17.beta.-Estradiol, progesterone, and 1,25-dihydroxyvitamin D3 did not affect or only weakly affected in vitro angiogenesis, which may be related to the lack of significant nuclear receptor expression. Although hMVEC express both thyroid hormone receptors .alpha. and .beta., no effect of thyroid hormone on tube formation was found. The effects of testosterone, dexamethasone, at-RA, and 9-cis RA on tube formation were accompanied by parallel changes in urokinase-type plasminogen activator (u-PA) expression, at both mRNA and antigen levels. Exogenous suppletion of the medium with single chain u-PA enhances tube formation in the in vitro model, whereas quenching of u-PA activity (but not of tissue-type plasminogen activator activity) or of u-PA binding to u-PA receptor by specific antibodies suppressed basal and retinoid-stimulated tube formation. Moreover, addn. of scu-PA to testosterone- or dexamethasone-treated hMVEC restored the suppressed angiogenic activity for a substantial part. Aprotinin, an inhibitor of plasmin activity, completely inhibited tube formation, indicating that the proteolytic properties of the u-PA/u-PA receptor complex are crucial in this process. The authors' results show that steroid hormones (testosterone and dexamethasone) and retinoids have strong, but opposite effects on tube formation in a human in vitro model reflecting pathol. angiogenesis in the presence of fibrin and inflammatory mediators. These effects can be explained by hormone-receptor-mediated changes in u-PA expression, resulting in enhanced local proteolytic capacity of the u-PA/u-PA receptor complex.
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:168790 CAPLUS
DOCUMENT NUMBER: 128:281273
TITLE: Differential expression of CYP1A1 and CYP1B1 in human breast epithelial cells and breast **tumor** cells
AUTHOR(S): Spink, David C.; Spink, Barbara C.; Cao, Joan Q.;

DePasquale, Joseph A.; Pentecost, Brian T.; Fasco, Michael J.; Li, Ying; Sutter, Thomas R.
CORPORATE SOURCE: New York State Department of Health, Wadsworth Center, Albany, NY, 12201-0509, USA
SOURCE: Carcinogenesis (**1998**), 19(2), 291-298
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human cytochromes P 450 1A1 (CYP1A1) and P 450 1B1 (CYP1B1) catalyze the metabolic activation of a no. of procarcinogens and the hydroxylation of 17.beta.-estradiol (E2) at the C-2 and C-4 positions, resp. The arom. hydrocarbon receptor (AhR) agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has a marked effect on estrogen metab. in MCF-7 breast-**tumor** cells by induction of these two enzymes. To investigate whether induction of CYP1A1 and CYP1B1 by AhR agonists and the assocd. increase in E2 metab. are common to all breast epithelial cells and breast-**tumor** cells, we detd. the effects of TCDD on E2 metab., and CYP1A1 and CYP1B1 mRNA levels in a series of non-**tumor** -derived breast epithelial (184A1 and MCF-10A) and breast-**tumor** (MCF-7, T-47D, ZR-75-1, BT-20, MDA-MB-157, MDA-MB-231 and MDA-MB-436) cell lines. In 184A1 cells, which did not express detectable estrogen receptor (ER) .alpha. mRNA, CYP1A1 mRNA and activity were induced by TCDD, and enhanced E2 metab. in TCDD-treated cells was predominantly E2 2-hydroxylation. In MCF-10A, MCF-7, T-47D, ZR-75-1 and BT-20 cells, which expressed varying levels of ER.alpha. mRNA, both CYP1A1 and CYP1B1 mRNA levels and rates of both E2 2- and 4-hydroxylation were highly elevated following exposure to TCDD. In MDA-MB-157, MDA-MB-231 and MDA-MB-436 cells, which did not express detectable ER.alpha. mRNA and generally displayed fibroblastic or mesenchymal rather than epithelial morphol., CYP1B1 induction was favored, and the rate of E2 4-hydroxylation exceeded that of 2-hydroxylation in TCDD-treated cells. These results show that breast epithelial cells and **tumor** cells vary widely with regard to AhR-mediated CYP1A1 and CYP1B1 induction, suggesting that factors in addn. to the AhR regulate CYP1A1 and CYP1B1 gene expression. In these cell lines, significant CYP1A1 inducibility was restricted to cultures displaying epithelial morphol., whereas CYP1B1 inducibility was obsd. in cells of both epithelial and mesenchymal morphol.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:516136 CAPLUS
DOCUMENT NUMBER: 129:211854
TITLE: Superinduction of wild-type p53 protein after 2-methoxyestradiol treatment of Ad5p53-transduced cells induces **tumor** cell apoptosis
AUTHOR(S): Mukhopadhyay, Tapas; Roth, Jack A.
CORPORATE SOURCE: Section of Thoracic Molecular Oncology, Department of Thoracic, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Oncogene (**1998**), 17(2), 241-246
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Because 2-methoxyestradiol (2-MeOE2) induces and stabilizes wild-type p53 protein (wt p53) in human lung **cancer** cell lines posttranscriptionally, we sought to study its effects on Ad5p53-transduced lung **cancer** cell lines at a low multiplicity of infection (1 MOI). Treating these cells with 2-MeOE2 resulted in superinduction of wt p53 protein expression followed by apoptosis, as shown by terminal deoxynucleotidyl transferase (TdT) staining, and upregulation of wt p53 expression, as shown by Western blot anal. When transduced with Ad5p53

alone at 1 MOI, the cell lines grew rapidly. Moreover, adenoviral-vector-mediated p53 gene transfer followed by 2-MeOE2 treatment caused 80% growth inhibition in the cell lines regardless of their p53 status. Thus, p53 superinduction and apoptosis after 2-MeOE2 treatment in Ad5p53-transduced cells appears to be a unique strategy with significant implications for **cancer** gene therapy.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:778968 CAPLUS

DOCUMENT NUMBER: 130:105451

TITLE: Inhibition of normal and experimental angiotumor endothelial cell proliferation and cell cycle progression by 2-methoxyestradiol

AUTHOR(S): Reiser, F.; Way, D.; Bernas, M.; Witte, M.; Witte, C.

CORPORATE SOURCE: Department of Surgery, The University of Arizona, Tucson, AZ, 85724, USA

SOURCE: Proceedings of the Society for Experimental Biology and Medicine (**1998**), 219(3), 211-216
CODEN: PSEBAA; ISSN: 0037-9727

PUBLISHER: Blackwell Science, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB With rapid growth and metab., aggressive **cancers** require an extensive vascular network, termed **tumor** angiogenesis. The body produces a variety of natural angiogenic inhibitors, among which is the mammalian estrogen metabolite, 2-methoxyestradiol (2-MeOE2). In this study, we compared the effects of 2-MeOE2 on a human umbilical vein cell line (HUVEC-C) and on an immortal, angiotumor-producing rat sinusoidal endothelial cell line (RSE-1). In vitro, the effects of varying concns. of 2-MeOE2 from 0.01-100.0 .mu.M were measured with cell counts and compared to control cells. HUVEC-C had an ED50 .apprx.3.5 .mu.M with .apprx.27% inhibition of cell growth whereas RSE-1 had an ED50 .apprx.2.2 .mu.M with .apprx.50% inhibition of cell growth compared with controls. The lowest concn. with maximal effect was 10.0 .mu.M 2-MeOE2 for both cell lines. Using this concn., flow cytometric anal. of cell cycles was performed with propidium iodide stained DNA of HUVEC-C and RSE-1 at 24 and 48 h. Both demonstrated a significant block at G2M of the cell cycle. At 48 h, HUVEC-C had 32% of cells in G2M (control = 9% G2M), and RSE-1 had 36% of cells in G2M (control = 18% G2M). These findings demonstrate a strong in vitro antiproliferative effect of 2-MeOE2 on normal dividing endothelial as well as angiotumor cells mediated through a cell cycle-specific block at G2M. The antiendothelial, antiangiotumor effect of 2-MeOE2 supports its potential as a therapeutic agent against solid organ **cancers**, benign or malignant vascular growths, and other pathol. states dependent on angiogenesis.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs 22 24 26 28 29 32 33 34 37 38

L5 ANSWER 22 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:498999 CAPLUS
DOCUMENT NUMBER: 129:118020
TITLE: 2-methoxyestradiol induces p53 independent apoptosis and inhibits growth of lung **metastases** of pancreatic **cancer**
AUTHOR(S): Schumacher, Guido; Kataoka, M.; Roth, J. A.; Mukhopadhyay, T.
CORPORATE SOURCE: Dep. Thoracic Cardiovasc. Surgery, M. D. Anderson Cancer Center, University Texas, Houston, TX, 77030, USA
SOURCE: Chirurgisches Forum fuer Experimentelle und Klinische Forschung (**1998**) 49-52
CODEN: CFEKA7; ISSN: 0303-6227
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: German
AB The inhibiting effect of 2-methoxyestradiol (2-ME) on pancreatic **cancer** was studied in vitro and in nude mice. In 3 out of 4 cell lines, 2 .mu.M 2-ME induced 50-90% growth inhibition after 48 h treatment. Under these conditions, 37-97% of the cells of these 3 lines underwent apoptotic cell death. Since all cell lines used harbor a p53 mutation, this apoptosis was p53 independent. The cell line MIAPaCa-2 was used for the in vivo-expt. After a daily oral administration of 1 mg 2-ME for 3 wk, the no. of lung **metastases** was decreased by 59%. No signs of toxicity were seen.

L5 ANSWER 24 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:40831 CAPLUS
DOCUMENT NUMBER: 130:177731
TITLE: 2-Methoxyestradiol, an endogenous metabolite of 17.beta.-estradiol, inhibits adipocyte proliferation
AUTHOR(S): Pico, Catalina; Puigserver, Pere; Oliver, Paula; Palou, Andreu
CORPORATE SOURCE: Laboratori de Biologia Molecular, Nutricio i Biotecnologia, Departament de Biologia Fonamental i Ciencies de la Salut, Universitat de les Illes Balears, Palma de Mallorca, Spain
SOURCE: Molecular and Cellular Biochemistry (**1998**), 189(1&2), 1-7
CODEN: MCBIB8; ISSN: 0300-8177
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of 2-methoxyestradiol (2ME), a naturally occurring mammalian metabolite of 17.beta.-estradiol, on adipocyte growth has been investigated in mouse brown adipose tissue precursor cells developed in primary culture. 2ME inhibits brown adipocyte proliferation in a dose-response manner (IC50 = 1.7 .times. 10-6M for DNA synthesis), with much higher potency than its hormone precursor 17.beta.-estradiol, and cells acquire the typical differentiated morphol. - more round with a higher content of triglycerides. 2ME causes similar effects in the immortal brown adipocyte **tumor**-derived hibernoma cell line HIB 1B and the immortal 3T3-F442A white adipocyte line. These findings suggest a possible role for 2ME in adipocyte proliferation, and probably in the differentiation process, entering the cells in the adipogenic program.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 26 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:483454 CAPLUS
DOCUMENT NUMBER: 127:91017
TITLE: Method and composition for treatment of pathological conditions associated with angiogenesis
INVENTOR(S): Fotsis, Theodore; Adlercreutz, Herman; Schweigerer, Lothar
PATENT ASSIGNEE(S): Germany
SOURCE: U.S., 10 pp., Cont.-in-part of U.S. Ser. No. 84,969, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5643900	A	19970701	US 1995-405776	19950317 <--

PRIORITY APPLN. INFO.: US 1993-84969 19930702
AB The present invention relates to a method and a compn. for the treatment of pathol. conditions assocd. with enhanced angiogenesis. The method comprises administering 2-methoxyestradiol to a subject in need of such treatment. 2-Methoxyestradiol also has potent pharmacol. properties in the treatment of solid **tumors**.

L5 ANSWER 28 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:122095 CAPLUS
DOCUMENT NUMBER: 126:207607
TITLE: Induction of apoptosis in human lung **cancer** cells after wild-type p53 activation by methoxyestradiol
AUTHOR(S): Mukhopadhyay, Tapas; Roth, Jack A.
CORPORATE SOURCE: M. D. Anderson Cancer Center, Univ. Texas, Houston, TX, 77030, USA
SOURCE: Oncogene (**1997**), 14(3), 379-384
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 2-Methoxyestradiol (2-MeOE2) treatment caused significant growth inhibition of H460 and A549 human lung **cancer** cell lines which contain wild-type p53. However, 2-MeOE2 had a little effect on the p53 neg. H358 and p53 mutated H322 cell lines. Western blot anal. indicated that 2-MeOE2 treatment resulted in an eightfold increase in the endogenous wild-type p53 protein, while the level of the mutant p53 protein remained unchanged. TdT staining indicated that following 2-MeOE2-mediated increases in wild-type p53 protein, cells bypass the G1-S checkpoint of the cell cycle with 30 to 40% undergoing apoptosis. Introduction of anti-sense wt-p53 into wt-p53 cells abrogated the 2-MeOE2 effect. A significant portion of lung **cancer** retains the wild-type p53 gene therefore, 2-MeOE2 may have therapeutic application.

L5 ANSWER 29 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:10247 CAPLUS
DOCUMENT NUMBER: 128:97804
TITLE: The mammalian metabolite, 2-methoxyestradiol, affects P53 levels and apoptosis induction in transformed cells but not in normal cells
AUTHOR(S): Seegers, Johanna C.; Lottering, Mona-Liza; Grobler, Christina J. S.; van Papendorp, Dirk H.; Habbersett, Robert C.; Shou, Yulin; Lehnert, Bruce E.
CORPORATE SOURCE: Department of Physiology, University of Pretoria, Pretoria, S. Afr.

SOURCE: Journal of Steroid Biochemistry and Molecular Biology (**1997**), 62(4), 253-267
CODEN: JSBBEZ; ISSN: 0960-0760
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The endogenous metabolite, 2-methoxyestradiol (2ME), is an inhibitor of tubulin polymn. and is therefore toxic to dividing fast-growing **tumor** cells. Transformed cells are not equally susceptible to the effects of 2ME. In this study the effects of 1-2 .mu.M doses of 2ME on cell cycle progression, apoptosis induction and on p53 levels were evaluated using flow cytometry in cells with different p53 status. No effect of 2ME was seen in normal human skin fibroblast strain HSF43 with wild-type (wt) p53. However, in SV40 T antigen transformed HSF43 cells (line E8T4), 2ME caused a prominent G2/M arrest, with subsequent micronuclei formation followed by apoptosis. Increased p53 levels were present in the G2/M cells. The results suggest that 2ME, being a microtubule poison, may release the bound p53 from T antigen, and that this p53 may enhance the apoptotic effects. Two lymphoblast cell lines derived from the same donor, TK6, expressing low levels of wt p53, and WTK1, expressing high levels of mutant p53, showed similar moderate responses to 2ME at 37.degree.C. The effects included enhanced apoptosis and a modest G2/M block. No increase in p53 levels was seen. However, at the permissive temp. of 30.degree.C marked increases in apoptosis and a prominent G2/M-phase block, similar to that seen in the E8T4 cells, were present in the WTK1 cells, indicating that the high levels of mutant p53 have now become functional, enhancing the apoptotic effects initiated by 2ME.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 32 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:39755 CAPLUS
DOCUMENT NUMBER: 126:127078
TITLE: Inhibition of angiogenesis and breast **cancer** in mice by the microtubule inhibitors 2-methoxyestradiol and taxol
AUTHOR(S): Klauber, Nancy; Parangi, Sareh; Flynn, Evelyn; Hamel, Ernest; D'Amato, Robert J.
CORPORATE SOURCE: Department Surgery, Children's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Cancer Research (**1997**), 57(1), 81-86
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 2-Methoxyestradiol (2-ME), an endogenous estrogen metabolite which disrupts microtubule function, has been shown to inhibit proliferating cells in vitro and suppress certain murine **tumors** in vivo. In vitro screening has detd. that breast **cancer** cell lines are most sensitive to inhibition by 2-ME. Addnl., 2-ME has been shown to inhibit angiogenesis in vitro. We tested whether 2-ME suppresses cytokine-induced angiogenesis in vivo and inhibits growth of a human breast carcinoma in severe combined immunodeficient mice. A model of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF)-induced corneal neovascularization in C57BL/6 mice was used to evaluate the antiangiogenic effects of 2-ME and other microtubule inhibitors such as Taxol, vincristine, and colchicine. 2-ME (150 mg/kg p.o.) inhibited bFGF and VEGF-induced neovascularization by 39% and 54%, resp. Taxol (6 mg/kg i.p.) inhibited bFGF and VEGF-induced neovascularization by 45% and 37%, resp. Vincristine (0.2 mg/kg i.p.) and colchicine (0.25 mg/kg i.p.) had no effect. Treatment with 2-ME (75 mg/kg p.o.) for 1 mo suppressed the growth of a human breast carcinoma in mice by 60% without toxicity. Recognition of the antiangiogenic and antitumor properties of 2-ME and

taxol may be crucial in planning clin. applications to angiogenesis-dependent diseases.

L5 ANSWER 33 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:127459 CAPLUS
DOCUMENT NUMBER: 126:126928
TITLE: Treatment and prevention of prostatic disease, including prostate **cancer** and benign prostatic hyperplasia, with compounds binding to sex hormone-binding globulin (SHBG), and method for therapeutic compound identification
INVENTOR(S): Smith, Roy G.; Rosner, William; Nakhla, Atif M.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA; St. Luke's/Roosevelt Hospital Center; Smith, Roy G.; Rosner, William; Nakhla, Atif M.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640150	A1	19961219	WO 1996-US8873	19960605 <--
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2222625	AA	19961219	CA 1996-2222625	19960605 <--
AU 9659841	A1	19961230	AU 1996-59841	19960605 <--
EP 833641	A1	19980408	EP 1996-917173	19960605 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 11507050	T2	19990622	JP 1996-501341	19960605 <--

PRIORITY APPLN. INFO.: US 1995-484633 19950607
WO 1996-US8873 19960605

AB A method for treating and preventing benign prostatic hyperplasia (BPH) and prostatic carcinoma involves administering a therapeutically effective amt. of a compd. which binds to SHBG and antagonizes the SHBG-mediated effects of both estradiol and 5.alpha.-androstan-3.alpha.,17.beta.-diol by preventing the binding of estradiol and 5.alpha.-androstan-3.alpha.,17.beta.-diol. Also disclosed are the compds. which bind SHBG and prevent the binding of estradiol and 5.alpha.-androstan-3.alpha.,17.beta.-diol, as well as a method of finding compds. which bind to SHBG and prevent the binding of estradiol.

L5 ANSWER 34 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:446732 CAPLUS
DOCUMENT NUMBER: 125:96100
TITLE: Monofunctional and/or polyfunctional polylysine conjugates for treatment of neural disorders, autoimmune diseases, and proliferative diseases
INVENTOR(S): Geffard, Michel
PATENT ASSIGNEE(S): Fr.
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9615810	A1	19960530	WO 1995-FR1517	19951117 <--
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2727117	A1	19960524	FR 1994-13861	19941118 <--
FR 2727117	B1	19970221		
CA 2205557	AA	19960530	CA 1995-2205557	19951117 <--
AU 9641811	A1	19960617	AU 1996-41811	19951117 <--
EP 792167	A1	19970903	EP 1995-940329	19951117 <--
EP 792167	B1	20010627		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10511643	T2	19981110	JP 1995-516622	19951117 <--
AT 202487	E	20010715	AT 1995-940329	19951117
ES 2161915	T3	20011216	ES 1995-940329	19951117
US 6114388	A	20000905	US 1997-836199	19970709
PRIORITY APPLN. INFO.:			FR 1994-13861 A	19941118
			WO 1995-FR1517 W	19951117

AB The use of polylysine for prepg. pharmaceutical compns. or combinations useful for treating neural degeneration, infectious, traumatic and toxic neuropathies, auto-immune degenerative diseases and proliferative diseases, is disclosed. Polylysine conjugates are also disclosed.

L5 ANSWER 37 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:687896 CAPLUS
DOCUMENT NUMBER: 126:14885
TITLE: 2-Methoxyestradiol arrests cells in mitosis without depolymerizing tubulin
AUTHOR(S): Attalla, Hesham; Makela, Tomi P.; Adlercreutz, Herman; Andersson, Leif C.
CORPORATE SOURCE: Department Clinical Chemistry, University Helsinki, Helsinki, FIN-00209, Finland
SOURCE: Biochemical and Biophysical Research Communications (**1996**), 228(2), 467-473
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The endogenous estrogen metabolite 2-methoxyestradiol (2-MeOE2) suppresses exptl. **tumor** growth in vivo and inhibits angiogenesis activity in vitro. Moreover, 2-MeOE2 has been obsd. to block mitosis in cell cultures. As high concns. of 2-MeOE2 prevent microtubule assembly in vitro, the mitotic arrest has been attributed to inhibition of tubulin polymn. Here we report that concns. of 2-MeOE2 that cause complete metaphasal arrest do not inhibit the assembly of mitotic spindles. In contrast to the chromosomal dispersal seen in cells arrested by the tubulin depolymg. drug colcemid, the chromosomes of cells treated with 2-MeOE2 remained in the metaphasal plate indicating a functional defect of the mitotic spindle. The 2-MeOE2 arrest resembles those induced by compds. affecting microtubule dynamics such as taxol and vinblastine. The 2-MeOE2 block is also similar to that induced by several anti-calmodulin agents. Given that metaphase to anaphase transition is a calmodulin-dependent step and our observation that 2-MeOE2 inhibits calmodulin activity in vitro, we suggest that the 2-MeOE2 metaphasal arrest may occur via inhibition of calmodulin.

L5 ANSWER 38 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:640895 CAPLUS
DOCUMENT NUMBER: 125:292016

TITLE: Inhibitors of angiogenesis in human urine

AUTHOR(S): Fotsis, Theodore; Pepper, Michael S.; Aktas, Erkan; Joussen, Antonia; Kruse, Friedrich; Adelcreutz, Herman; Waehaelea, Kristina; Hase, Tapio; Montesano, Roberto; Schweigerer, Lothar

CORPORATE SOURCE: Children's University Hospital, University of Heidelberg, Heidelberg, 69120, Germany

SOURCE: NATO ASI Series, Series A: Life Sciences (**1996**), 285(Molecular, Cellular, and Clinical Aspects of Angiogenesis), 213-227
CODEN: NALSDJ; ISSN: 0258-1213

PUBLISHER: Plenum

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with .apprx.50 refs. on the authors' work in screening urine of human subjects consuming a diet rich in plant products for anti-angiogenic compds. The authors identified the isoflavonoid genistein, the endogenous estrogen metabolite 2-methoxyestradiol and metabolites of flavonoids that show inhibitory activities against angiogenesis. Irresp. of whether or not these substances play any physiol. role in humans, they might be suitable as pharmacol. agents for treatment of solid malignant **tumors** and other angiogenic diseases.